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VENOM IMMUNOTHERAPY: COMPARISON OF "RUSH" VS "CONVENTIONAL" SCHEDULES

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Twenty-three patients aged five to 52 years with good clinical histories of severe systemic reactions to hymenoptera stings confirmed by skin tests and RAST levels were treated with specific insect venoms. A more conventional, slow, bi-weekly schedule was used to determine whether they could be as successfully treated as those in earlier studies employing the "Rush desensitization" approach. It was also hoped these subjects would experience fewer untoward reactions. Comparisons of IgG (anti-hyaluronidase and phospholipase) levels pretreatment and after top dose (100 mcg) in all cases showed greater than three-fold rise, indicating protection. RAST IgE rose in most cases and plateaued by six months. Nineteen patients were restung to verify protection. Untoward reactions to injections were low (13%) and easily controlled. The authors conclude that the use of specific freeze dried insect venoms in a slow dose schedule is safe and effective in protecting severely sensitized individuals.

Introduction

RECENT STUDIES have clearly shown that immediate hypersensitivity type reactions to stinging insects of the hymenoptera class are mediated by specific IgE antibodies directed against venom proteins.[1,2] The use of specific venom immunization in severely sensitized patients is now accepted as the treatment of choice by allergists in the United States as well as most other countries throughout the world.[3]

Presently available venom for commercial usage is freeze dried after collection and then reconstituted at the time it is to be injected. It is recommended that it be given in a "modified Rush" method whereby two or three injections are given in one day, 30 minutes apart.[4] Each injection is two to 10 times greater than the previous, enabling the patients to reach a dose of 100 mcg, equivalent to two stings, within eight weeks (Table I). It is felt that at this dosage protection occurs as evidenced by a significant rise of blocking (IgG) antibodies and by a diminished reaction when accidentally or intentionally restung.[5,6]

Table I. Rush Regimen for Venom Immunotherapy.

Day	Total dose (mcg)
1	0.001, 0.01, 0.1
8	0.1, 0.5, 1.0
15	1.0, 5.0, 10
22	10, 20
29	20, 30
35	30, 30
43	40, 40
50	50, 50
57	100
64	100
78	100
99	100
monthly	100

The incidence of systemic reactions with this Rush method is substantial (14-20%).[3] The patient must spend relatively long periods in the physician's office and this routine is sufficiently different from a conventional bi-weekly or weekly regimen that is customarily used to administer other antigens. For these reasons we embarked on this study to determine whether insect freeze dried venoms* could be safely and effectively administered to a group of severely sensitized individuals utilizing a slower, more conventional immunizing schedule.

Experimental Design

A. Patient Data

Twenty-three patients, ages five to 52 years with good clinical histories of severe systemic reactions to a stinging insect, were selected from our practice. There were 16 males and seven females. All patients were skin test positive to one or more venoms and most had significant positive RAST scores. All *in vivo* and *in vitro*

*Kindly supplied by Pharmacia Inc., Piscataway, N.J.

(Pharmacia). Some patients had been previously treated with whole body extracts. None were pregnant at the time the study was started and patients with hepatic, cardiovascular renal or other serious diseases were excluded.

B. Skin Testing

Patients were withdrawn from all antihistamine-containing drugs for 72 hours prior to testing. Each patient was tested intradermally with honey bee, yellow jacket, white hornet, yellow hornet and wasp venoms. Testing was begun by injecting 0.05 ml of 0.001 mcg/ml (1:1,000,000,000 W/V) of each venom into the forearm. A patient was considered sensitive if he or she exhibited at least a 1+ reaction (10 mm erythema and 5 mm wheal). If no reaction occurred at the 1.0 mcg/ml (1:1,000,000 W/V) concentration, the patient was considered nonreactive.

Table II. Slow (Conventional) Regimen For Venom Immunotherapy.

Week	Injection	Total dose (mcg)
1	1	0.01
	2	0.02
2	3	0.03
	4	0.04
3	5	0.06
	6	0.1
4	7	0.2
	8	0.3
5	9	0.4
	10	0.6
6	11	1.0
	12	2.0
7	13	3.0
	14	4.0
8	15	6.0
	16	10
9	17	20
	18	30
10	19	40
	20	60
11	21	80
	22	100
12	23	100
13	24	100
15	25	100
18 monthly	26	100

Table III. Pharmacia Freeze Dried Venom Study.

Skin Test Results				
Bee	Y.J.	WFH	YFH	WASP
22	3	3	3	3

Table IV. Pharmacia Freeze Dried Venom Study.

Reactions to injections

A. Local 20/23 = 87%.
B. Systemic 3/23 = 13%.

1. Pt. #9: itching palm, feet, face, difficulty swallowing at 50, 80 and 100 mcg.
2. Pt. #16: dizzy, angioedema lips, nausea, shortness of breath, itching at 60 + 70 mcg.
3. Pt. #21: generalized itching and hives, shortness of breath, at 60 and 80 mcg.

C. In Vitro Assays

1. IgE Measurement. Specific IgE measurements were performed via the RAST method utilizing cyanogen bromide activated paper discs and reagents prepared by Dr. Donald R. Hoffman.[7] Results are expressed in percentage of binding. Measurements were done at the beginning of the study, when reaching top dose and at one year.

2. IgG Antibodies to Hyaluronidase and Phospholipase A. Specific IgG antibodies were measured to Phospholipase A and hyaluronidase by the double antibody technique; 25 mcl of 1:10 dilution of serum is added to 0.1 or 0.2 mcg of I^{125} labeled Phospholipase A or Hyaluronidase and incubated for three hours. To this is then added 100 microliters of anti IgG, incubated one hour at room temperature and then overnight at 4°C. The mixture is then centifuged, washed and counted. The results are expressed in micrograms of antigen bound per ml. of serum.

In vitro antibody measurements were performed at the beginning of the study, when reaching top doses, (11-16) weeks), three months later and at one year. At the same time blood was drawn for CBC, sedimentation rate, platelet count and serum chemistries, and a urinalysis was performed.

D. Immunization Schedule (Table II)

Patients were treated to all venoms to which they gave a positive skin test in a bi-weekly manner at three to four-day intervals. Patients were started one dilution below the weakest giving a positive test. If no systemic or large local reaction was noted, the next injection would be increased by 25% to 50% until a total dosage of 100 micrograms was tolerated. This was estimated to take 11 to 16 weeks to accomplish. Patients allergic to the venoms of all five insects were given three separate injections, one containing bee venom, the second mixed vespids (yellow jacket, yellow and white faced hornet) and the third wasp.

After top dose was reached the patients were rapidly spread out to one-, two-, three- and finally four-week intervals. All adverse reactions to injections and any accidental (field) stings were carefully monitored.

E. Intentional Stinging

After one year of treatment and provided that a two-fold or greater rise was observed in IgG antibody titers, patients were given the option of being intentionally stung. This was performed in the emergency room of a local hospital with an intravenous line dripping and with all emergency resuscitation measures available. One investigator and an anesthesiologist were in attendance. Patients were monitored carefully for any changes in vital signs or development of anaphylaxis for a period of 60 minutes after the sting.

Results

Skin Testing

Of 23 patients, 22 reacted to bee venom and three to

yellow jacket, white faced hornet and wasp (Table III). No adverse reactions were encountered during the skin test procedures.

Reactions to Injections: see Table IV

A. Local Reactions: Twenty patients (87%) experienced local reactions to the injections. Most were mild (less than 10 mm erythema and/or induration) and transient but a few were large enough to cause swelling of the entire upper extremity.

B. Systemic Reactions: Systemic reactions occurred in three patients (13%). No systemic reactions occurred at doses less than 50 mcg. All of these reactions were milder than the systemic reaction the patient had experienced when stung. All patients with systemic reactions were eventually able to reach top dose.

C. RAST Results (Table V): Eighteen of 22 patients (82%) with positive skin tests to bee venom had positive RAST scores. All three patients with positive skin tests to yellow jacket had positive RAST scores but only two of three (66%) skin test patients sensitive to white faced hornet and one of three (33%) skin test sensitive to paper wasp had antibodies detectable by RAST. No yellow hornet RAST reagents were available.

D. IgE and IgG Antibody Responses to Immunotherapy:

1. IgE: IgE levels (Figure 1) rose an average of 40% by the time top dosage was reached in all but five patients. Levels in all but one patient then began falling so that by one year they approximated pre-treatment levels.

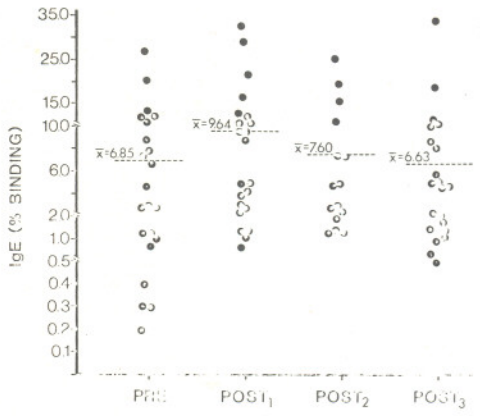

Figure 1. Venom injections (IgE response).

2. IgG: IgG antibodies to hyaluronidase (Figure 2) and Phospholipase A (Figure 3) showed an average two- to three-fold rise in all patients. Levels were close to peak by the time the patients had received three 100 mcg doses. IgG levels remained elevated throughout the first year in all patients.

There was no difference in IgG (or IgE) response in those individuals experiencing local or systemic reactions or those subsequently reacting to intentional sting.

Reaction to Stings

A. Accidental Stings. Four patients experienced accidental stings during the course of the study. None experienced systemic reactions although all had large locals. Two were stung early into the study and two toward the end.

B. Intentional Stings. Nineteen of the study group underwent intentional stings. Eighteen were stung with honey bees and one with a paper wasp. Fifteen tolerated the sting without incident. Two experienced mild transient urticaria and cough 15 minutes after a bee sting. The symptoms spontaneously subsided within 10

Table V. Pharmacia Freeze Dried Venom Study.

RAST results —	Correlation with Skin Tests
HB	18/22
Y.J.	3/3
W.F.H.	2/3
Y.H.	ND
WASP	1/3

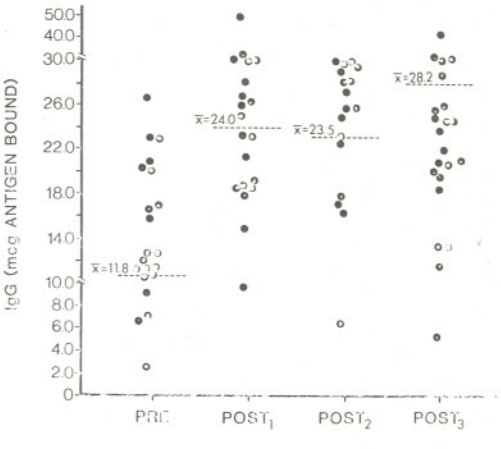

Figure 2. Venom immunotherapy IgG (anti-hyaluromidase) response.

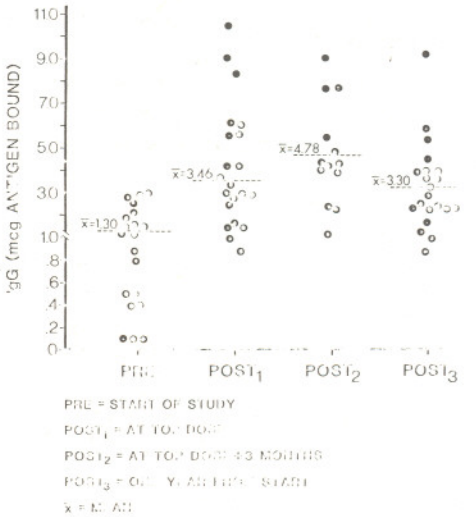

Figure 3. Venom immunotherapy IgG (anti-phospholipase-A).

minutes without need for treatment.

Two patients (10.5%) experienced reactions to bee stings requiring emergency treatment with adrenalin and Benadryl®. Both patients experienced generalized urticaria and angioedema with bronchospasm. The reaction occurred approximately 25 minutes after the sting and in both cases the reactions experienced were milder than previously noted to accidental stings.

Toxicology Studies

No patients experienced any abnormalities in CBC, sedimentation rate, urinalysis, platelet count of chemistry panel testing.

Discussion

The use of "pure" hymenoptera venom in the treatment of severely sensitive individuals has now become accepted by most physicians. One of the major concerns to practicing allergists has been the unique schedule that is recommended for administration.

The "Rush method" advocated (Table I) in the package insert as well as in the literature[3] has the advantage of allowing patients to possibly reach maintenance doses in as few as 50 days. However, they must be prepared to spend 60 to 90 minutes in a physician's office, receive several (three to nine) injections per session and experience a substantial reaction rate previously reported to be as high as 25%. For children, an added objection could be made for the amount of time away from school or after school activities.

The Rush method is sufficiently different from usual methods that it may serve to make many allergists reluctant to utilize venom injections for fear that it may confuse their staff. This may explain, in part, the results of a recent survey purporting to show that as many as 60%[4] of practicing allergists are still not using insect venoms.

A theoretical objection raised by Valentine and co-workers to a slower immunizing method is that it might enhance the specific IgE response and dampen the IgG response over what they accomplished with the Rush method, thus making a patient more vulnerable to an accidental sting. Our antibody measurements do not support this concern.

We conclude that the use of a slower immunizing schedule in the treatment of patients allergic to hymenoptera venom:

1. Is associated with the same or perhaps fewer systemic reactions than the currently recommended Rush method.
2. Produces adequate levels of IgG antibodies.
3. Affords protection against an accidental or intentional re-sting.
4. Offers those patients who need venom immunotherapy an alternative to the Rush method without compromising safety or efficacy.

In this study we have not attempted to answer why some patients with a good blocking antibody response are still symptomatic when re-stung, whether those with large local reaction are setups for more severe reactions in the future and what effect long-term immunizing will have. These questions will be the object of future studies.

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